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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 11/000,309
Filing Date: November 30, 2004
Appellant(s): YONEDA ET AL.

Aaron Rabinowitz
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 15 May 2009 appealing from the Office action mailed 20 June 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is substantially correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

US 2004/0209354	Mathies et al	21 October 2004
US 2004/0037739	McNeely et al	26 February 2004
US 6,833,242	Quake et al	21 December 2004
US 6,875,620	Schembri et al	05 April 2005
US 2004/0038388	Yamamoto et al	26 February 2004
US 20020001845	Klaerner et al	03 January 2002
US 2003/0062310	Zare et al	03 April 2003
US 2002/0168652	Werner et al	14 November 2002
US 6,368,871	Christel et al	09 April 2002
US 6,156,273	Regnier et al	05 December 2000

Mathies is directed to a microfluidic chip comprising a plurality of vias and a functionalized porous polymer monolith capable of purifying an analyte sample solution.

McNeely is directed to a microfluidic chip comprising a detection unit in the form of a microarray, and an observation port for detecting analytes disposed at the microarray.

Quake is directed to a microfluidic chip configured for the detection and analysis of a nucleic acid sample comprising a plurality of fluid channels characterized by depths less than 10 microns and greater than 1 micron.

Schembri is directed to a microfluidic chip comprising a microarray that includes a plurality of different probes capable of binding to different target analytes.

Yamamoto is directed to a microfluidic chip comprising a microarray composed of a plurality of neatly arranged spots, wherein each spot contains up to about 50,000 probes, and is separated from other spots by at least 100 microns and at most 500 microns.

Klaerner is directed to a microfluidic chip comprising a microarray that implements glycidyl methacrylate functional monomers to covalently attach probes to a polymer layer.

Zare is directed to a microfluidic chip comprising a porous polymer monolith formed during a photocatalytic step involving UV light and Irgacure 1800.

Werner is directed to a microfluidic chip comprising a microarray formed between a base substrate and a cover substrate.

Christel is directed to a microfluidic chip comprising fluid channels that contain microposts designed for manipulating and controlling fluids.

Regnier is directed to a microfluidic chip comprising a fluid channel that splits to form a micromanifold to increase the contact area of the channel.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior

art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Apellant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11, 55-64, 66, 68-77, and 111-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathies (US 20040209354) in view of McNeely (US 20040037739) and Quake (US 6833242).

With respect to claims 1 and 61-63, Mathies discloses a microfluidic chip comprising a plurality of flow channels (Figure 1:321, 323, 325, 327). Figure 8 depicts

an embodiment of the invention wherein each channel contains a plurality of capture chambers (Figure 8:801, 803, 805, 807) that are useful in the purification of biological analytes. This is disclosed in paragraphs [0073]-[0075]. Paragraphs [0080]-[0082] state that the chambers may include a functionalized, porous, polymer monolith, and that antibody or nucleic acid probes may be immobilized upon the polymer monolith or the surface of the chambers in order to promote binding. The functionalized, porous, polymer monolith is highly crosslinked and comprises pores permitting fluid communication through the polymer monolith. In Figure 12 and paragraph [0091], Mathies teaches that a capture chamber (Figure 12:1201) is surrounded by a plurality of vias (Figure 12:1211 and Figure 12:1213) through which fluids can be introduced and withdrawn. Mathies, discloses that the polymer monolith is used for the purification and isolation of biochemical analytes before detection occurs. Mathies, however, teaches that detection is accomplished using capillary electrophoresis instead of a microarray.

McNeely discloses a microfluidic chip that utilizes a plurality of microarrays (Figure 27:154) as mean by which to detect various biochemical analytes in a sample solution. This is disclosed in paragraphs [0086]-[0088] and throughout the entire reference. Paragraph [0155] teaches that optical detection windows are further incorporated in the apparatus.

Mathies and McNeely are analogous art because they are from the same field of endeavor regarding microfabricated chips that are used to analyze biological samples.

At the time of the invention, it would have been obvious to substitute the capillary electrophoresis system disclosed by Mathies for a detection system dependent on the

use of microarrays. Accordingly, it would have also been apparent to include an observation port in the apparatus disclosed by Mathies since many microarray hybridization systems involve fluorescence detection. McNeely teaches in paragraphs [0004]-[0008] that the use of microarrays to detect biochemical analytes is well known in the art (a point with which Appellant) concurred in the interview scheduled 10/27/06), and that microarrays are effective in performing complex analyses of samples since they are capable of carrying out multiple detection reactions simultaneously. In the biomedical field, the use of microarrays for detection purposes is recognized as an effective way to diagnose various medical conditions, determine predisposition of patients to diseases, and perform DNA fingerprinting. In paragraphs [0033] and [0034], McNeely teaches that microarrays are also advantageous detection devices since they produce reliable and reproducible results, and can be automatically processed. In paragraphs [0157]-[0160], McNeely additionally indicates that it is known in the art to utilize microarrays in fluid communication with various pre-processing modules such as purification units based on differential affinity matrices. Therefore, it would have been obvious to utilize a system of microarrays to detect analytes following purification in the apparatus disclosed by Mathies.

The combination of Mathies and McNeely stills fails to disclose Appellant's claimed invention because neither reference teaches the use of microchannels having depths in the range of 1 to 10 microns.

Quake discloses a microfluidic substrate that comprises a plurality of microfluidic channels capable of moving biological analytes to and from a detection area. Column 24, lines 45-55 state that the microchannels preferably have a diameter of 2 to 5 microns.

Mathies, McNeely and Quake are analogous art because they are from the same field of endeavor regarding microfluidic detection systems.

At the time of the invention, it would have been obvious to ensure that the microfluidic channels disclosed by Mathies were characterized by a depth in the range of 1 to 10 microns. Quake teaches in column 22, line 30 to column 24, line 44 that it is known in the art to construct microfluidic channels of this size within a substrate to facilitate sample flow and mixing. The selection of appropriate channel dimensions is considered to be a result effective variable that is optimized through routine experimentation. If it was determined that channel depths of 1 to 10 microns proved effective in the apparatus of Mathies, it would have been obvious to utilize microchannels of this size.

With respect to claims 2-6, 8, 9, and 11, Mathies, McNeely and Quake disclose the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 103 rejection above. In addition, Mathies and McNeely teach that the microarray comprises at least one probe, is capable of binding to a nucleic acid, oligonucleotide, protein, antigen, or antibody target. Mathies and McNeely disclose that nucleic acid probes are capable of hybridizing with nucleic acid targets.

With respect to claims 7, 10, 59, 60, 76, and 77, Mathies, McNeely and Quake disclose the apparatus set forth in claims 5, 6, 56, and 75 as set forth in the 35 U.S.C. 103 rejection above. Although Mathies and McNeely do not expressly disclose the use of oligo-T and cDNA as probes and/or targets, it would have been obvious to do so. Both references teach that there are no restrictions to implementing essentially any type of biological polymer within the apparatus as long as it is capable of selectively binding. The references simply fail to expressly itemize cDNA and oligo-T. The use of oligo-T and cDNA as probes or as targets in hybridization reactions is well known in the art, and could have effectively been included in the apparatus disclosed by Mathies and McNeely.

With respect to claims 64 and 66, Mathies, McNeely and Quake disclose the apparatus set forth in claim 63 as set forth in the 35 U.S.C. 103 rejection above. Mathies teaches in paragraph [0083] that the functionalized, porous, polymer monolith is crosslinked with ethylene dimethacrylate, which serves to help immobilize probes on the pore surface.

With respect to claim 68, Mathies, McNeely and Quake disclose the apparatus set forth in claim 63 as set forth in the 35 U.S.C. 103 rejection above. Mathies teaches in paragraph [0080] that the polymer monolith comprises pores in the range of 10-20 microns. One of ordinary skill in the art would understand that pore ranges of 10-20 microns and those “smaller than about 10 microns” would perform identically during

binding events. See *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985).

With respect to claims 69 and 70, Mathies, McNeely and Quake disclose the apparatus set forth in claim 63 as set forth in the 35 U.S.C. 103 rejection above. Although Mathies and McNeely do not expressly disclose void fractions and operating pressures, it would have been obvious to construct the polymer monolith to meet the claimed limitations. Varying the void fraction of the monolith to achieve the most favorable design is simply the optimization of result effective variables that could be pursued using routine experimentation. In the absence of new or unexpected results, it would have been obvious to ensure that the polymer monolith comprised a void fraction of less than 50% and was able to operate at pressures between 100 and 3,000 PSI. This would guarantee that the monolith would have had ample surface area to promote target binding, and would have been functional under pressure conditions that are typical of microarrays. See *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980).

With respect to claims 71-75, Mathies, McNeely and Quake disclose the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 103 rejection above. In addition, Mathies teaches in paragraphs [0081]-[0083] that the functionalized porous polymer monolith comprises at least one functional group for binding a sample compound. Mathies states that azlactone, acrylate, and amide function groups may be linked to the porous monolith in order to promote binding to proteins, antibodies, and

antigens. In paragraphs [0079] and [0086], Mathies discloses nucleic acid probes binding to nucleic acid targets. Although Mathies does not expressly disclose that the functionalized polymer monolith is covalently bonded to the substrate, it would have been obvious to do so since it is beneficial and well known in the art to covalently bond probes and linker molecules to a support. Since the polymer monolith acts as a linker molecule by binding to the probes, and since the polymer monolith surface is easily functionalized, it would have been apparent to covalently bind the polymer monolith to the substrate.

With respect to claims 111-113, Mathies, McNeely and Quake disclose the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 103 rejection above. The capture chamber disclosed by Mathies containing the functionalized, porous, polymer monolith may intrinsically function as a derivatization reservoir that facilitates the trapping of target nucleic acids. Mathies discloses the use of protein ligands and protein receptors in paragraphs [0073]-[0079].

With respect to claim 114, Mathies, McNeely and Quake disclose the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 103 rejection above. In addition, Mathies discloses the use of mobile, monolith valves capable of controlling fluid flow in paragraphs [0036]-[0044].

<u>Claims 16-25, 31-44, and 51-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathies (US 20040209354) in view of McNeely (US 20040037739) and Quake (US 6833242) as applied to claims 2 and 11, and further in view of Schembri (US 6875620).</u>

With respect to claims 16-18, Mathies, McNeely and Quake disclose the apparatus set forth in claim 11 as set forth in the 35 U.S.C. 103 rejection above, however do not expressly disclose that the apparatus comprises a plurality of different probes that are capable of binding to different targets.

Schembri discloses a substrate (Figure 1:13) comprising a plurality of tiles (Figure 1:9) that contain immobilized probes upon their surfaces. In column 3, line 40 to column 4, line 40, Schembri states that an individual substrate may include a variety of different probes (Figure 1:11) that are each capable of binding to a unique target.

Mathies, McNeely, Quake and Schembri are analogous art because they are from the same field of endeavor regarding the assembly of microarrays.

At the time of the invention, it would have been obvious to immobilize a variety of different probes within the apparatus disclosed by Mathies in order to promote binding to a number of different targets. In column 2, lines 1-15, Schembri states that it is beneficial to incorporate probes comprising nucleic acids, proteins, polysaccharides, and lipids into the binding region with the intention of facilitating the simultaneous detection of a variety of analytes. In this way, the same device may be used to thoroughly evaluate a sample.

With respect to claims 19-25, 31-35, 43, 44, and 51-54, Mathies, McNeely and Quake disclose the apparatus set forth in claims 2 and 11 as set forth in the 35 U.S.C. 103 rejection above. In addition, McNeely seems to indicate in the Figures and in paragraphs [0086]-[0088] that the probes are disposed as spots fashioned in an ordered arrangement. However, this is not clearly disclosed in the specification.

Schembri discloses a microarray in which a plurality of probes (Figure 1:7) is arranged upon a plurality of tiles (Figure 1:9). The tiles function as “spots” that define affinity binding regions. This is disclosed in column 3, line 40 to column 4, line 40. Column 3, lines 4-8 indicate that the tiles are between 40 and 250 microns wide. It is apparent from Figure 1 that the tiles are arranged in an orderly fashion and planarly arranged in two dimensions. Figure 2 discloses an embodiment in which the tiles are arranged in three dimensions. Column 3, lines 30-39 and column 4, lines 7-26 disclose that linker molecules (Figure 1:5) are used to covalently bind the probes to the device.

At the time of the invention, it would have been obvious to arrange the probes as spots upon the substrate of the apparatus disclosed by Mathies. This would have been desirable because it would have defined distinct binding regions each comprising specific probes designed to capture specific targets. This would have provided an ordered and organized way to screen a sample solution for the presence of a plurality of certain analytes. Making the width of the spots 10 to 250 microns would have guaranteed that the spots were large enough to promote efficient detection, and small enough to allow the addition of many different spots. Varying the sizes of the spots to achieve the most favorable design is simply the optimization of result effective variables

that could be pursued using routine experimentation. In the absence of new or unexpected results, it would have been obvious to size the spots according to the claimed limitations. See *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980).

With respect to claims 36-42, Mathies, McNeely, Quake and Schembri disclose the apparatus set forth in claim 35 as set forth in the 35 U.S.C. 103 rejection above. In addition, Mathies teaches that capture chambers (Figure 8:801, 803, 805, 807) are disposed within at least one microchannel (Figure 8:821). In light of the Schembri reference, these capture chambers would contain a plurality of spots comprising a plurality of biological probes. From the Figure, it is clear that the microchannel comprises a rectangular serpentine path with first and second sections being separated by a wall. Although specific channel dimensions are not expressly disclosed, it would have been obvious to ensure that the width and length of the microchannel and sidewalls were adjusted to optimize hybridization and detection.

Claims 12-15, 19, 25-35, 43-46, and 48-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathies (US 20040209354) in view of McNeely (US 20040037739) and Quake (US 6833242) as applied to claim 2 and 11, and further in view of Yamamoto (US 20040038388).

With respect to claims 12-15, 19, 25-35, 43-46 and 51-54, Mathies, McNeely and Quake disclose the apparatus set forth in claim 2 and 11 as set forth in the 35 U.S.C. 103 rejection above, however do not expressly disclose that the microarray comprises a

plurality of neatly arranged spots, each containing up to about 50,000 probes and separated from each other by at least 100 microns and at most 500 microns.

Yamamoto discloses a substrate (Figure 4:410) comprising a plurality of probes arranged as a plurality of spots (Figure 4:420) across the substrate. Paragraph [0105] gives an example in which a spot contains 2,500 probes and another example in which a spot contains 48,400 probes. Probes are systematic arranged within the spots in rows and columns. For example, paragraph [0105] teaches that the spot containing 2,500 probes may be arranged as a square comprising 50 rows and 50 columns of probes. Paragraph [0090] states that the spots are physically separated by a distance with the range of 100 to 1,500 microns. Paragraph [0116] discloses an embodiment in which the probes are disposed with microwells (Figure 4:440). Paragraph [0053] indicates that linker molecules are used to covalently bind the probes to the substrate.

At the time of the invention, it would have been obvious to immobilize a significant number of probes (1,000 to 50,000) at each spot within the apparatus disclosed by Mathies. This would have ensured that the target analytes would have had ample opportunity to react with the array. It would have further been obvious to ensure that the spots were adequately spaced apart (100 to 1,500 microns) in order to clearly distinguish and locate binding events. Arranging the probes in a plurality of spots on the substrate would have been beneficial because it would have allowed one to group probes together in different arrangements in an effort to better analyze results. Varying the number of probes within the spots and the distances between spots to achieve the most favorable design is simply the optimization of result effective variables that could

be pursued using routine experimentation. In the absence of new or unexpected results, it would have been obvious to construct the spots according to the claimed limitations. See *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980).

With respect to claims 48-50, Mathies, McNeely and Quake disclose the apparatus set forth in claim 2 and 11 as set forth in the 35 U.S.C. 103 rejection above. Although Mathies, McNeely, and Yamamoto do not expressly disclose that the plurality of probes comprise a disordered arrangement, it would have been obvious to construct the apparatus in this way. Randomly placing the plurality of probes requires less accuracy and precision during microarray construction, and therefore is likely to increase manufacturing speed and decrease cost. Unless an ordered arrangement is required by a specific application, randomly disposing probes across the substrate would not decrease the likelihood of hybridization or the effectiveness of detection procedures.

Claim 65 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mathies (US 20040209354) in view of McNeely (US 20040037739) and Quake (US 6833242) as applied to claim 64, and further in view of Klaerner (US 20020001845).

Mathies, McNeely and Quake disclose the apparatus set forth in claim 64 as set forth in the 35 U.S.C. 103 rejection above, however do not expressly disclose the use of glycidyl methacrylate.

Klaerner discloses a microarray device comprising a substrate covered by a polymer layer. The polymer layer is composed of a number of probes that are capable of binding to specific biological target molecules. Paragraphs [0126] and [0133] state that glycidyl methacrylate functional monomers are utilized in order to covalently attach probes to the polymer layer.

Mathies, McNeely, Quake and Klaerner are analogous art because they are from the same field of endeavor regarding microarrays.

At the time of the invention, it would have been obvious to crosslink functionalized glycidyl methacrylate monomers to the porous polymer monolith disclosed by Mathies. Klaerner teaches in paragraphs [0126] and [0133] that it is well known in the art to utilize glycidyl methacrylate as a means to covalently attach biological probes to a substrate. Since Mathies already teaches that a similar mono-ethylenically unsaturated monomer (ethylene dimethacrylate) is effective in binding certain probes to the surface of the polymer monolith, it would have been obvious to incorporate similar monomer compounds, such as glycidyl methacrylate, to complete the same task.

Claims 67 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mathies (US 20040209354) in view of McNeely (US 20040037739) and Quake (US 6833242) as applied to claim 62, and further in view of Zare (US 20030062310).

Mathies, McNeely and Quake disclose the apparatus set forth in claim 63 as set forth in the 35 U.S.C. 103 rejection above. In addition, Mathies teaches in paragraphs

[0081] and [0082] that UV light is used to catalyze polymer crosslinking. Mathies, however, does not expressly disclose the use of Irgacure 1800 during the UV activation.

Zare discloses a separation column which comprises a porous polymer matrix, and is used for the separation of biomolecules. Paragraphs [0069]-[0072] state that a photoinitiator is used to catalyze the polymerization of organic monomers to form the porous matrix. Paragraphs [0078]-[0081] specifically indicate that UV light and Irgacure 1800 are used during this catalytic step.

Mathies, McNeely, Quake and Zare are analogous art because they are from the same field of endeavor regarding the use of photoinitiators to catalyze polymerization reactions in order to form a porous polymer matrix designed for the capture of biomolecules.

At the time of the invention, it would have been obvious to use UV light and Irgacure 1800 photoinitiators to aid in the formation of the functionalized porous polymer monolith. Zare teaches in paragraph [0080] that catalytic polymerization reactions involving Irgacure 1800 and UV are beneficial because they require a short preparation time, do not require high temperatures, and produce a polymer product characterized by a high mechanical strength. Furthermore, this procedure is advantageous because it allows one to have control over what the pore sizes, placement, and length of the polymer product will be.

Claims 78-90, 93, 94, 96, 97, and 106-110 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathies (US 20040209354) in view of McNeely (US

<u>20040037739) and Quake (US 6833242) as applied to claim 1, and further in view of Werner (US 20020168652).</u>

With respect to claims 78-83, 86-90, 93, 94, 96, 97, 106, and 107, Mathies, McNeely and Quake disclose the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 103 rejection above, however do not expressly disclose that the microarray and the functionalized porous polymer monolith are disposed between a base substrate and a cover substrate.

Werner discloses microarray capture zones (Figure 3:148) that are disposed between a base substrate (Figure 3:146) and a cover (Figure 3:130). In Figures 8-11 and in paragraphs [0072]-[0075], Werner teaches that the microarray probes may be disposed on a top surface of the cover, or on the surface of the base substrate. In paragraphs [0096] and [0098], Werner discloses that the cover may be made clear in order to permit optical interrogation of the capture zones. A plurality of vias (Figure 3:132 and Figure 3:134) are disposed within the cover and are in fluid communication with the microarray. In paragraph [0082], Werner teaches that the vias are also capable of being in fluid communication with external fluidic devices (Figure 18:176) such as micropipettes carrying solutions to be analyzed. An adhesive layer (Figure 3:136) is used to bond the cover to the base substrate, and the microarray device comprises at least one microchannel (Figure 3:140) and reservoir (Figure 3:144).

Mathies, McNeely, Quake and Werner are analogous art because they are from the same field of endeavor regarding the construction of microfluidic devices comprising biological probes.

At the time of the invention, it would have been obvious utilize a base substrate and a cover substrate in order to define a microfluidic system to contain the microarray and the functionalized porous polymer monolith disclosed by Mathies. The use of these sandwich type arrangements is well known in the art, and is beneficial because sandwich arrays allow one to easily construct a system of microchannels and microwells between the cover and base. Furthermore, the fluidic system can be handled much easier and is less susceptible to contamination when the polymer monolith and the microarray are disposed between a cover and a base.

With respect claims 84 and 85, Mathies, McNeely, Quake and Werner disclose the apparatus set forth in claim 86 as set forth in the 35 U.S.C. 103 rejection above. In addition, Werner teaches an arrangement in which a plurality of channels (Figure 3:142) are provided, each with its own set of microarrays (Figure 3:148) and vias (Figure 3:132). In this way, microarrays and vias are not in fluid communication with each other if they belong to separate channel structures. At the time of the invention, it would have been obvious to create a microarray system in which each of the individual hybridization areas were not fluidly connected. This would have been desirable if it was necessary to complete a plurality of separate screening procedures at once on a variety of different sample solutions.

With respect claims 108-110, Mathies, McNeely, Quake and Werner disclose the apparatus set forth in claim 86 as set forth in the 35 U.S.C. 103 rejection above. In

addition, McNeely teaches in paragraph [0155] that observation ports may constitute windows in the cover, and may be disposed across one or more channels and/or chambers of the device. At the time of the invention, it would have been obvious to ensure that the cover portion comprised at least one such observation port in order to allow visual inspection of the microarrays or polymer monoliths so that hybridization at specific probes may be detected.

Claims 91 and 98-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathies (US 20040209354) in view of McNeely (US 20040037739), Quake (US 6833242) and Werner (US 20020168652) as applied to claims 87 and 89, and further in view of Christel (US 6368871).

Mathies, McNeely, Quake and Werner disclose the apparatus set forth in claims 87 and 89 as set forth in the 35 U.S.C. 103 rejection above, however do not expressly disclose specific microchannel dimensions, or that the apparatus further comprises microposts.

Christel discloses a sample chip comprising a body portion including a plurality of microchannels formed therein. Column 4, lines 1-2 state that the invention is designed for manipulating, controlling, and moving fluids on a microscale, and column 2, lines 7-12, Figures 1e-h, and Figure 2 teach that the microchannels are created in essentially any pattern or size. Christel teaches in column 6, lines 8-9 that these channels are typically 10-1,000 μm deep and 50 μm wide, and that fluids containing biological objects are introduced the channels via inlet and outlet ports, according to column 7, lines 57-

64. The exact dimensions of the channel may be altered to meet the needs of specific applications. Column 7, lines 35-37 and column 11, lines 21-23 describe that a cover portion is bonded upon a body portion to effectively form a seal over the microchannels. Column 2, lines 46-55 and column 7, lines 10-20 describe that microchannels, as well as a number of microposts, are formed out of the chip by using a variety of etching, photolithography, and micromachining techniques. Column 2, lines 13-26 indicate that the microposts may selectively interact with and retain desired molecules, and column 8, lines 60 to column 9, line 7 teach that an electric field may be applied as an extra measure to hold molecules at the microposts. Individual microposts may be of any shape or size, according to column 7, lines 47-48, and are visually represented in Figures 1a-d. The microposts intrinsically may be fashioned at any sample chamber or at any point along the microchannels. The microposts may be utilized to enhance mixing.

Mathies, McNeely, Quake, Werner, and Christel are analogous art because they are from the same field of endeavor regarding microfluidic chips designed for the analysis of biological fluids.

At the time of the invention, it would have been obvious to incorporate a plurality of microposts into the apparatus disclosed by Mathies, McNeely, Quake and Werner in order to enhance mixing of the fluid flowing through the microfluidic device. In column 4, lines 10-42, Christel teaches that mixing is a critical component of many biochemical analytical protocols, and can be enhanced by optimizing microchannel design and through the addition of microposts into the reaction area. Mixing is often difficult to

achieve in microfluidic devices, and microposts offer an efficient alternative to more traditional macroscale methods. It would have further been obvious to ensure that the depth and width of the channels disclosed by Mathies, McNeely, and Werner were in the ranges of 10 to 100 microns and 100 to 10,000 microns, respectively. Microfluidic devices comprising microchannels are desirable because they can carry out a thorough analysis using very small amounts of fluid, thereby reducing the costs associated with the purchase of reagents. It would have been obvious to optimize the depth and width of the channels carrying the biological targets to the microarrays for each specific procedure through routine experimentation.

Claims 92 and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathies (US 20040209354) in view of McNeely (US 20040037739), Quake (US 6833242) and Werner (US 20020168652) as applied to claims 90 and 93, and further in view of Regnier (US 6156273).

Mathies, McNeely, Quake and Werner disclose the apparatus set forth in claims 90 and 93 as set forth in the 35 U.S.C. 103 rejection above. In addition, McNeely discloses an embodiment in which microarray reservoirs (Figure 19:194) are connected to a micromanifold (Figure 19:166). This is described in paragraphs [0098], [0099], [0116], and [0117]. McNeely, however, does not disclose that the micromanifold is in communication with a single chamber.

Regnier discloses a microfluidic system designed to separate analytes from a liquid stream. Regnier teaches that microfluidic channels (Figure 1:12) are periodically

split in order to enhance the separation process and form a micromanifold (Figure 6:99). This is disclosed in column 3, line 36 to column 4, line 10 and column 11, lines 13-52.

Mathies, McNeely, Quake, Werner, and Regnier are analogous art because they are from the same field of endeavor regarding microfluidic biological systems.

At the time of the invention, it would have been obvious to utilize the micromanifold disclosed by Regnier at the reservoirs of the microarray disclosed by Mathies, McNeely, Quake and Werner. In column 12, lines 16-25, Regnier teaches that splitting a fluid channel into a plurality of individual offshoots is beneficial in microfluidic systems because it increases the contact area of the channel, which in turn allows one to more effectively capture and retain analytes in solution. This would have been desirable in the design of microarrays, since immobilized probes must come into physical contact with a desired target in order to detect its presence. Regnier further teaches that a micromanifold would have ensured that the linear velocity of the fluid and the pressure drop were constant at all points in the system. In this way, the incorporation of a micromanifold into the device proposed by Mathies, McNeely, and Werner prior to the reservoir and microarray would have advantageously equalized the pressure distribution within the structure.

(10) Response to Argument

I. Claims 1-11, 55-64, 66, 68-77, and 111-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathies (US 20040209354) in view of McNeely (US 20040037739) and Quake (US 6833242).

Appellant's principle arguments are

(a) Quake's channels of 2-5 microns in depth are plainly contrary to McNeely's teaching that channels be more than 15 microns in depth. It is improper to combine references where the references teach away from their combination.

The channel depth measurements set forth in Quake do not teach away from the channel depth measurements set forth in McNeely. McNeely discloses that the depth channels must be at least 15 microns only because the depth of the channels is dependent entirely on the height of a gasket. McNeely teaches in paragraph [0084] that "[t]he height of the reaction chamber 640 is defined by the thickness of the gasket 404." This is apparent from Figure 3 below.

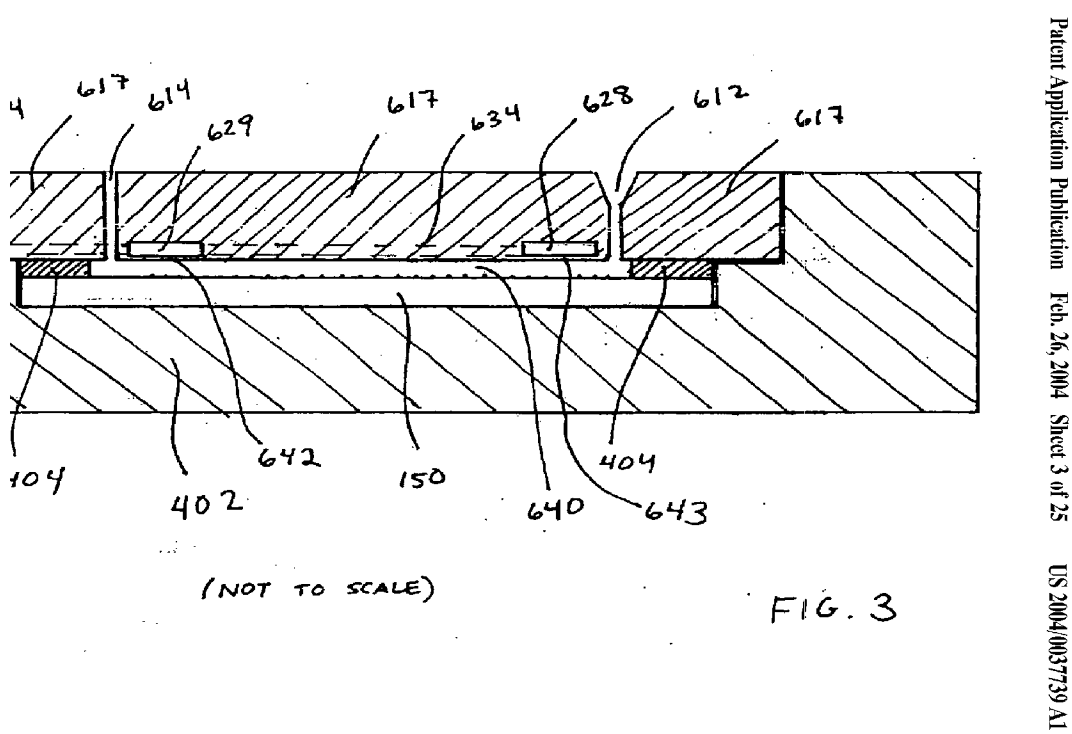

FIG. 3

The McNeely reaction chamber/channels are formed by a gasket 404 sandwiched between a base substrate 402 and a coverslip 617, and accordingly, the structural

integrity of the McNeely system is dependent on maintaining the structural integrity of the gasket 404 (i.e. the gasket can't be too small because otherwise it would exhibit structural nonuniformities). In fact, McNeely expresses an interest in even smaller microarray channels/chambers in paragraph [0084] ("while it is desirable to have a small reaction chamber volume..."), but cannot obtain smaller sizes due to his reliance on providing a gasket between the base substrate and coverslip.

However, the reaction chambers/channels of the Quake system are not created using a gasket at all, and therefore are capable of being formed with depths lower than 15 microns, and more preferably between 2 and 5 microns. Instead of using a gasket, Quake teaches in column 30, lines 43-57 that the channels/chambers are etched directly into a silicon substrate, and that the etched features are subsequently covered by a glass coverslip.

Quake would only teach away from McNeely if Quake, like McNeely, required a gasket to form microchannels and microchambers. Since Quake does not require a gasket, Quake is drawn to a different biochip manufacturing process, is not concerned with the same structural problems (i.e. gasket nonuniformity), and therefore does not teach away from the requirements of McNeely.

At is also noted that Appellant does not assert that the microarray of McNeely would be rendered inoperable if incorporated into the 2-5 micron channels of Quake. Since the microarray probes disclosed by McNeely are composed of relatively short nucleic acid fragments, they certainly could be positioned within a channel less than 15 microns in depth and still serve to effectively bind to an analyte in solution. In fact,

Quake teaches in column 24, lines 8-55 that his 2-5 micron channels are fully capable of accommodating and processing large DNA molecules (200 kpbs).

(b) The McNeely reference's requirement that channels be more than 15 microns in depth teaches away from Appellants' claim 1 recitation that the channel depth be in the range from about 1 micron to less than 10 microns.

Again, the McNeely reference only requires channels to be more than 15 microns in depth because McNeely cannot reliably produce a gasket that is less than 15 microns in height. The primary reference Mathies, like Quake, does not disclose the use of a gasket to define the depth of a reaction chamber or reaction channel, but instead teaches that chambers and channels are etched directly into the top surface of a substrate which is then covered using a coverslip. See Mathies paragraphs [0036]-[0039]. Accordingly, one of ordinary skill would not look to the McNeely reference for determining how big or how small to form channels in Mathies because the construction of McNeely is limited due to its dependence on the use of a gasket – a structural feature not even required by Mathies.

One of ordinary skill would understand from McNeely that microarrays are common and effective features typically utilized within microfluidic chips, but one of ordinary skill would have to look elsewhere to determine exactly how to incorporate those features into the Mathies apparatus. More specifically, one would look to the Quake reference, which discloses a similar etching technique as taught by Mathies. Quake, as described above, clearly discloses in column 24, lines 45-55 that it

microchannels should be etched into a base substrate so that they are 2-5 microns in depth.

(c) The declaration submitted by Dr. West is evidence of unexpected results. The claimed invention exhibits superior performance because it allows for detection in only about 5 minutes, whereas hybridization in McNeely is "typically performed overnight" (McNeely at [0153]).

The declaration filed on March 25, 2008 is deficient because it fails to compare the results of the invention of the instant application with results obtained by the systems of Mathies and McNeely. Rather, paragraph 6 of the declaration merely states that the results are "unexpectedly superior to those of alternative devices in the field." It is unclear what these alternative devices are, or if they even resemble the cited prior art at all. The fact that the device of the instant application obtains results faster than some unnamed detection apparatus offers little insight as to whether detection in 5 minutes is sufficiently superior to the results expected from the use of a microarray in the apparatus of Mathies.

Appellant contends that no side-by-side experimentation is necessary to compare results obtained by the instant invention and those expected from the prior art combination because McNeely states that hybridization (the biochemical reaction necessary before optical detection is possible) is performed "overnight." From this, Appellant concludes that McNeely is incapable of producing detectable results until about 8 hours have expired. This conclusion is misplaced. The fact that McNeely

leaves the microarray out "overnight" in no way means that the microarray hybridization reaction actually requires 8 hours to be completed. It could be completed within an hour, and just sit there for the rest of the night. It could be completed in less time. McNeely is silent as to exactly how much time the reaction requires for completion, and Appellant has not provided any evidence that microarrays of the prior art require approximately 8 hours to achieve detectable results.

Furthermore, it is noted that the declaration of unexpected results appears to not be commensurate in scope with the claimed apparatus. The “Results” section of the provided journal article in the declaration states that the alleged unexpected results are obtained using a microarray located within a microchannel that is 15 microns in depth (“Fabricated Chips (Figure 1:B) contained an open channel that is etched 15 μm into the top surface of the microfluidic device…” and "The shallow serpentine micro channel (15 μm height X 300 μm wide) greatly reduces the hybridization time…”) This height of 15 microns is greater than the claimed range of 1-10 microns, and is equivalent to the microchannel height set forth in McNeely. It is not understood how Appellant obtains unexpected results if the microarray is structurally the same as that set forth by McNeely. If Appellant's unexpected results are to be believed, they must be due to structural features present in the tested device of the declaration, but not present as limitations in the claimed invention of the instant application.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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